UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/857,332	09/17/2001	Nigel C. Phillips	02511-015US	3254

23370 7590 12/17/2002

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
SUITE 2800
ATLANTA, GA 30309

EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
3635	

DATE MAILED: 12/17/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,332	PHILLIPS ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

This Action is in response to the communication filed on 9/30/02, as Paper No. 12. Claims 33, 41, 49 and 57 have been amended. Claims 33-64 are pending in the application and are examined herein.

Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Response to Amendment and Arguments

The rejection of claims set forth in the previous Office Action have been withdrawn in view of the claim amendments and arguments set forth in the communication filed 9/30/02. However, upon further consideration, it is determined that the claims are not enabled for the treatment of cancer for the reasons set forth below.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 33-64 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) A method of inhibiting melanoma cell growth comprising direct administration to melanoma cells:

(a) a composition comprising Mycobacterium phlei DNA complexed on Mycobacterium phlei cell wall (MCC) and a pharmaceutical acceptable carrier; and

(b) a chemotherapeutic agent to an animal of human having melanoma, wherein the composition and the chemotherapeutic agent administered to the animal or human having melanoma display an anti-cancer synergism;

2) A method of inhibiting melanoma cell growth comprising direct administration to melanoma cells:

(a) a composition comprising Mycobacterium phlei DNA and a pharmaceutical acceptable carrier; and

(b) a chemotherapeutic agent to an animal of human having melanoma, wherein the composition and the chemotherapeutic agent administered to the animal or human having melanoma display an anti-cancer synergism;

3) A method of inhibiting melanoma cell growth comprising direct administration to melanoma cells:

(a) a composition comprising mycobacterial DNA complexed on a mycobacterial cell wall (BCC) and a pharmaceutical acceptable carrier; and

(b) a chemotherapeutic agent to an animal of human having melanoma, wherein the composition and the chemotherapeutic agent administered to the animal or human having melanoma display an anti-cancer synergism;

4) A method of inhibiting melanoma cell growth comprising direct administration to melanoma cells:

(a) a composition comprising mycobacterial DNA (B-DNA) and a pharmaceutical acceptable carrier; and

(b) a chemotherapeutic agent to an animal of human having melanoma, wherein the composition and the chemotherapeutic agent administered to the animal or human having melanoma display an anti-cancer synergism;

does not reasonably provide enablement for methods of treating any type of cancer by administering a combination of 1) mycobacterial DNA (including M. phlei DNA)/mycobacterial DNA complexed on BCC (including M. phlei DNA complexed on MCC), and 2) a chemotherapeutic agent; wherein the combination treatment is administered by any means other than direct administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to methods of treating cancer in a human or animal wherein said methods comprise administering a pharmaceutical composition comprising mycobacterial DNA or mycobacterial cell wall complex (including M. phlei DNA and M. phlei cell wall complex) and a chemotherapeutic agent wherein the combination treatment exhibits an anti-cancer synergism.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the Invention:

As mentioned above, the claims are drawn methods of treating cancer in a human or animal wherein said methods comprise administering a pharmaceutical composition comprising mycobacterial DNA or mycobacterial cell wall complex a chemotherapeutic agent wherein the combination treatment exhibits an anti-cancer synergism. Therefore, the general nature of the invention is cancer treatment and, more specifically, combination immunotherapy/chemotherapy for cancer treatment.

Breadth of the Claims:

The claims are drawn to treating any type of cancer in any animal, including humans, by administering a composition comprising the combination of: 1) a composition comprising a mycobacterial DNA (B-DNA) (including M. phlei DNA), or mycobacterial cell wall complex (MCC) (including M. phlei cell wall complex); and 2) any chemotherapeutic agent, wherein the composition can be administered by any route including systemic administration and direct administration to a tumor.

The state of the prior art and unpredictability of the art:

The prior art indicates that there are a number of problems related to pharmaceutical administration of mycobacterial DNA/cell wall compositions for the treatment of cancer. For example, Morales (Journ. Urol. 153:1706-1710; 1995) indicates the general unpredictability of mycobacterial compositions for the treatment of cancer by stating, "successful immunotherapy of solid neoplasms has been an elusive goal" (see p1706, first paragraph). In addition to the general unpredictable nature of mycobacterial compositions for the treatment of cancer, Morales also teaches a number of specific problems.

It is respectfully pointed out that the claims encompass administering a mycobacterial DNA or cell wall complex and a chemotherapeutic agent either directly or by a generalized administration to subject. However, the prior art indicates that not all administrations of MCC/B-DNA would be effective. For instance, Morales teaches that although administration of mycobacteria phlei cell wall (MCW) by intratumoral administration results in regression of established prostate tumors, "the response, however, depends initially on the route of administration. The intraperitoneal route was found to be not only in effective, but detrimental." (See p. 1709, bottom, first column). Furthermore Morales teaches, "the intraperitoneal administration of MCW did not alter tumor-growth kinetics... the rats receiving MCW by this routs became lethargic, anorexic and exhibited considerable hair loss." (See p. 1707, middle of first column).

Morales also indicates that the efficacy of mycobacterial cell wall/DNA complexes on tumor treatment varies depending on tumor size and/or the dose administered. Specifically, Morales teaches,

> "Two additional factors were found to be critical in the treatment of R3327-H with MCW: dose of the drug and tumor volume... 500ug [i.p.] weekly dose x 5 was ineffective regardless of tumor size... Perhaps the most important observation of the study is the crucial importance of tumor volume at the onset of treatment... A cure rate of 50% was reached with a single course of treatment in the group of animals harboring smaller lesions... No cure rates were recorded in any of the rats with larger tumors." (See p. 1709, second column, emphasis added for clarity).

Therefore, Morales indicates that although mycobacterial formulations can be effective treatments by direct administration of the formulation to small tumors (i.e. tumors $<2.2cm^3$), the treatment is not effective for curing larger tumors.

Working Examples and Guidance provided:

As mentioned above, the claims encompass the treatment of any type of cancer, including solid tumors (such as melanoma) as well as non-solid tumors (such as leukemia). The working examples presented in the specification only indicate the treatment of melanoma cells by directly administering the compounds to the melanoma cells in vitro.

Specifically, the specification discloses that treating B16 melanoma cells in culture with MCC+mitomycin C (MMC), MCC+5-Fluorouracil (5-FU), and MCC+cisplatin (CISP). The specification indicates that these treatments result in a synergistic effect with regard to inhibition of melanoma cell division in vitro only compared to the administration of the individual compounds (see Figures 2-4). However, there is no indication in the specification that any type of cancer cell other than melanoma cells were responsive the combination of drugs. Therefore, lacking evidence to the contrary, it is impossible to predict that the same treatments would have

the exact same synergistic effect on any type of cancer cell other than melanoma. Furthermore, although the combination treatments disclosed have been shown to have synergistic effect on inhibiting melanoma cell division in vitro, there is no indication that the treatments would have an identical synergistic effect on inhibiting melanoma cell division (or any other type of cancer cell) in vivo.

Figures 6 and 7 disclose that the treatment of melanoma cells with MCC alone can induce chromosomal breakdown (Figure 6) and induction of Caspase 1 (Figure 7), two characteristics of apoptosis. However, Figure 8 indicates that there was no difference between untreated control melanoma cells and MCC treated melanoma cells when cytotoxicity was assayed. Although mycobacterial cell wall complex (or DNA) treatment alone can activate caspase 1 and induce chromosomal breakdown, there is no indication that MCC treatment results in any cytotoxic effect on cancer cells. Therefore, there is no indication that the claimed combination treatments would result in killing of any cancer cell either in vitro or in vivo, a feature critical to treating cancer.

Furthermore, there is no guidance in the specification indicating how to effectively administer the compounds to different types of tumors. Considering the teaching of the prior art that 1) intraperitoneal (i.p.) administration of MCW is ineffective for treating prostate tumors in vivo, 2) direct administration of MCW to large tumors was ineffective at eliminating these tumors, 3) the lack or evidence indicating that the claimed treatments would have an identical effect on melanoma cells in vivo, and 4) the lack or evidence indicating that the claimed treatments would have an identical effect on any other cell type in vitro or in vivo; it is clear that one of skill in the art would require additional experimentation in order to effectively use the

claimed method to treat any type of cancer (such as prostate tumors) by any route of administration (such as i.p. administration), with a reasonable expectation of success.

Quantity of Experimentation:

As mentioned above, the claims encompass treating (including eliminating) any type of cancer by administering (via any route) a composition comprising a combination of a mycobacterial cell wall/DNA complex and any chemotherapeutic agent to the cancer cell. Considering the number of obstacles recognized in the art which must be overcome for successful treatment of any type of cancer, and the fact that the only positive correlating evidence disclosed in the specification is the treatment of melanoma cells in culture wherein the treatments only resulted in synergistic inhibition of melanoma cell division; additional experimentation is required in order to effectively use the method claimed.

For instance, additional experimentation is required to 1) characterize the effects of the combination treatments on cancer cell types other than melanoma, 2) characterize the effects of the treatments on melanoma and other types of cancers in vivo, 3) overcome the problems with types of administration other than direct administration, 4) overcome the problem of treating large tumors in vivo, 5) indicate that the claimed treatments could have cytotoxic effects on any type of tumor cell in vitro and in vivo. This would require, initially, testing the claimed treatments on small and large melanoma tumors in vivo, in order to determine if the combination treatments would be effective for treating melanoma tumors in vivo. Furthermore, additional experiments are required to enable the method for treating any type of cancer in vivo. This would require testing small and large tumors of different tumor types in vivo by direct and indirect administration, as well as in vivo testing of the treatments on non-solid cancers such as

leukemia. The additional experiments on non-melanoma cells would first have to be confirmed on cells in cell culture, followed by in vivo testing in animal models and then in clinical trials in humans.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of therapeutic mycobacterial compositions for cancer treatment recognized in the art, the breadth of the claims, the lack of working examples and guidance provided, and the high degree of skill required, it is concluded that the amount of experimentation required to effectively use the broadly claimed method is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
December 16, 2002